REMARKS

Formal Matters

Claims 34, 42, 45, 66, 69, 77, 85, 86, and 88-91 were examined in the Office Action under reply. Claims 45, 69 and 88 were indicated as allowable and the remaining claims were rejected under 35 U.S.C. §103(a). The rejections are respectfully traversed as discussed further below.

Claims 45, 69 and 88 have been rewritten in independent form and new claim 92 has been added. Support for new claim 92 can be found in the specification, for example, at page 4, lines 23-30; page 26, lines 27-29; and page 28, lines 17-19. Entry of the new claim is respectfully requested.

Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Applicants note with appreciation the withdrawal of the previous rejections of claims 34-36, 37, 42-44, and 66-68 under 35 U.S.C. §103(a), as well as the withdrawal of finality of the previous Office Action.

Applicants reiterate their request that claims 80-82, drawn to methods of making the cell line of claim 77 (Group IV) and claims 83 and 84 drawn to methods of using the cell line of claim 77, be rejoined and examined upon allowance of claim 77 drawn to the cell line of Group IV.

35 U.S.C. § 103

A. Major in view of Michalak and Valenzuela, further in view of Ono, Choo, and Chapman

Claims 34, 42, and 66 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Major et al. (J. Virol. 69:5798-5805; hereinafter "Major") in view of the reference of Michalak et al. (J. Gen. Virol. 78:2299-2306;

hereinafter "Michalak") and Valenzuela et al. (Bio/Technology 3:323-326; hereinafter "Valenzuela 1"), further in view of Ono et al. (Nuc. Acids Res. 11:1747-1757; hereinafter "Ono"), Choo et al. (Proc. Natl. Acad. Sci. U.S.A. 88:2451-2455; hereinafter "Choo"), and Chapman et al. (Nuc. Acids Res. 19:3979-3986; hereinafter "Chapman"). Major, Michalak and Valenzuela are applied for reasons of record. The Office Action correctly notes the references do not disclose the specific sequences of the encoded proteins comprising SEQ ID NO:7 or a variant thereof that are encompassed by the claims (Office Action, page 3). Nor do the references disclose a sequence comprising a fusion between the truncated HCV E2 proteins and HBV S antigen with a human tissue plasminogen activation (tPA) signal sequence at the N-terminus (Office Action, pages 3-4). Ono and Choo are cited for demonstrating "that the SAg and E2 sequences used in the fusion of SEQ ID NO:7 were known in the art." Office Action, page 4. Chapman allegedly teaches "a vector for the expression of heterologous proteins in mammalian cells" and the use of a tPA signal sequence in the vector. Office Action, page 4. The Office argues:

> Those of ordinary skill in the art would have had a reasonable expectation of success to substitute the HBV and HCV sequences of Ono and Choo for those in the previous references as the different sequence would represent functional equivalents of the viral sequences used in those references. Those of ordinary skill in the art would also have been motivated to use the vector of Chapman because the vector is disclosed as useful for the expression of heterologous sequences, such as the fusion protein suggested by the other references. (Office Action, pages 4-5, bridging paragraph.)

The Office action also alleges it would have been obvious to one of ordinary skill in the art to use linker and spacer sequences in making the fusion protein (Office Action, page 5). Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the Office Action's supporting remarks on the following grounds.

The decision by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007) recently reaffirmed the viability of the four factual inquiries underlying an obviousness analysis provided in *Graham v. John Deere*, 148 USPQ 459, 467 (U.S. 1966). These factors include: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of

secondary considerations. Moreover, the Supreme Court in *KSR* recognized that the "teaching, suggestion, or motivation" analysis provides a helpful insight in determining whether the claimed subject matter is obvious. This analysis is provided in MPEP 2142.

In particular, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Both the teaching or suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art, not in applicant's disclosure. See, *e.g.*, *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Based on the foregoing, applicants respectfully submit the Office has failed to establish a *prima facie* case of obviousness.

Major fails to teach or suggest a nucleic acid encoding a fusion protein combining an HBsAg polypeptide and an E2 polypeptide, as claimed. Major instead teaches a nucleic acid encoding HBsAg and a portion of an HCV **core** antigen. Major also fails to teach or suggest an immunogenic composition comprising such a nucleic acid. In particular, Major states that the core region was chosen for incorporation into fusion proteins because it is "well conserved between genotypes" (see page 5798, col. 1).

Nor do any of the secondary references teach or suggest the claimed invention. Michalak pertains to the biochemical characterization of truncated forms of E2 to determine the effect of C-terminal deletions on E2 secretion and protein folding. Michalak fails to describe or suggest a nucleic acid encoding E1 or E2 antigens fused to any HBV sequence. Furthermore, Michalak fails to describe any immunogenic compositions comprising nucleic acids encoding HCV or HBV antigens.

Valenzuela also fails to fill the gaps. Valenzuela does not describe or suggest immunization using HCV antigens. Rather, Valenzuela pertains to immunization against herpes simplex virus utilizing a vector expressing a hybrid particle comprising HBsAg and herpes simplex virus surface antigens. Valenzuela is silent with regard to HCV fusions.

Ono and Choo disclose the complete genome sequences of HBV and HCV, respectively; however, neither reference describes or suggests combining HBV and HCV viral sequences in fusions.

Chapman describes CMV vectors, but has nothing to do with the claimed invention. Chapman is silent regarding HBV or HCV, chimeric fusions, immunogenic compositions or immunization with VLPs comprising HBsAg.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. As stated in *KSR*, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, page 14. The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). Thus, a rejection cannot be based on the presence of individual components of the claimed invention in several different references. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner. This, the Office has failed to do.

Additionally, the Office has failed to provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." *KSR*, page 13. In fact, the evidence is to the contrary. The cited art fails to provide evidence that a nucleic acid molecule which encodes a fusion protein comprising HBsAg and the E2 sequence of SEQ ID NO:7 or a sequence having at least about 90% sequence identity thereto, as claimed, could be used successfully to elicit an immunological response against HCV and induce formation of HBV virus particles.

Thus, the stated combination fails to render the claimed subject matter obvious, and withdrawal of the rejection under 35 U.S.C. § 103(a) is in order.

B. Jacobs in view of Major, Michalak, and Valenzuela, further in view of Ono, Choo, and Chapman

Claim 77 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Jacobs et al. (U.S. Patent No. 6,306,625; hereinafter "Jacobs") in view of the references of Major, Michalak, and Valenzuela 1, and further in view of the references of Ono, Choo, and Chapman, as applied against claims 34, 42, and 66. Applicants respectfully traverse.

The combination of Major, Michalak, Valenzuela 1, Ono, Choo, and Chapman is described above. Jacobs fails to provide the missing links. Jacobs does not describe or suggest any cell line producing VLPs containing a chimeric antigen comprising an HCV immunogenic polypeptide. As discussed above, none of the references of Major, Michalak, Valenzuela, Ono, Choo, and Chapman teach or suggest nucleic acids encoding a fusion combining, in particular, HBsAg and an E2 polypeptide or a cell line expressing virus-like particles comprising HBsAg in addition to a chimeric antigen comprising HBsAg linked to an HCV immunogenic polypeptide.

Thus, as with the combination above, the Office appears to be selecting bits and pieces of the cited references based on hindsight reconstruction. Applicants submit there is no combination of the cited references that renders the claimed subject matter obvious, and withdrawal of the rejection under 35 U.S.C. § 103(a) is in order.

C. Major, Michalak, and Valenzuela 1, in view of Ono, Choo, and Chapman, further in view of Jacobs, De Wilde, Valenzuela 2, and Mountford

Claims 85 and 86 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Major, Michalak, and Valenzuela 1, in view of the references of Jacobs, Ono, Choo, and Chapman, as applied against claim 77, and further in view of the references of De Wilde et al. (U.S. Patent No. 5,928,902, hereinafter "De Wilde"), Valenzuela et al. (U.S. Patent No. 4,722,840; hereinafter "Valenzuela 2"), and Mountford et al. (Proc. Natl. Acad. Sci. U.S.A. 91:4303-4307; hereinafter "Mountford"). Applicants respectfully traverse the rejection under 35 U.S.C. § 103.

As discussed above, Major, Michalak, Valenzuela 1, Jacobs, Ono, Choo, and Chapman fail to teach or suggest any nucleic acid encoding a fusion protein comprising HBsAg and an HCV E2 antigen. Furthermore, Major, Michalak, and Valenzuela 1 fail to teach or suggest a vector comprising a nucleic acid sequence which encodes HBsAg in addition to a nucleic acid sequence which encodes a fusion protein comprising HBsAg linked to an HCV immunogenic polypeptide.

De Wilde, Valenzuela 2 and Mountford do not cure the defects of the combination. De Wilde pertains to immunization against malaria infection, and accordingly, teaches a hybrid protein comprising the CS protein of *P. falciparum*. De Wilde fails, however, to teach any nucleic acid or vector encoding a fusion of HBsAg to any HCV immunogenic polypeptide, nor does De Wilde provide any motivation for using any HCV antigen.

Valenzuela 2 similarly fails to disclose or suggest any nucleic acid or vector encoding a chimeric antigen comprising HBsAg linked to an HCV immunogenic polypeptide.

Mountford merely describes bicistronic constructs in general and has nothing to do with expression of HCV/HBV fusions or VLPs.

Accordingly, the above combination is deficient, and withdrawal of the rejection under 35 U.S.C. § 103(a) is in order.

D. Major, Michalak, and Valenzuela 1, in view of Ono, Choo, and Chapman, further in view of Maertens or Flint

Claims 89-91 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Major, Michalak, and Valenzuela 1, in view of the references of Ono, Choo, and Chapman, as applied against claims 34, 42, and 66, and further in view of the references of Maertens et al. (U.S. Patent No. 6,890,737, hereinafter "Maertens") or Flint et al. (J. Virol. 73:6782-6790; hereinafter "Flint"). The Office alleges "the teachings of the previously described references render obvious nucleotide sequences encoding fusion proteins sharing at least 90% identity to SEQ ID NO:7." (Office Action, page 7.) The Office further argues "the references suggest nucleic acids encoding fusions varying from SEQ ID NO:7 only in the inclusion of a

linker sequence at residues 304 and 305 of the fusion protein (the inclusion of which would have been obvious to those of ordinary skill in the art), and by the additional inclusion of residues 371-383 of the HCV polyprotein." (Office Action, page 7.)

Maertens is said to teach truncated forms of E2 terminating at residue 661 and that E2 begins at residue 384 of the HCV polyprotein. Flint is cited for allegedly teaching a fusion of E2 with another viral envelope protein such that E2 is incorporated onto the surface of another virus-like particle and the expression and inclusion into such a particle of a fusion of the truncated HCV protein comprising residues 384-661. The Office Action concludes it would have been obvious "to modify the teachings of Major, Michalak, and Valenzuela so as to include only the E2 coding regions, and thus result in a fusion protein comprising residues 383-661 of the HCV polyprotein." (Office Action, page 8.) Applicants respectfully traverse.

As discussed above, Major, Michalak, Valenzuela 1, Ono, Choo, and Chapman fail to teach or suggest any nucleic acid encoding a fusion protein comprising HBsAg and an HCV E2 antigen, nor any vector or immunogenic composition comprising such a nucleic acid. The secondary references of Maertens and Flint do not fill the gaps.

Maertens focuses on the purification of HCV E1 and E2 proteins and the use of compositions comprising these proteins in immunization against HCV. Maertens fails to describe or suggest any immunogenic compositions comprising nucleic acids (claim 91). Nor does Maertens describe or suggest combining E1 and E2 in fusions with any HBV proteins, or any nucleic acid or vector encoding such fusions.

Flint pertains to chimeric E2 antigens containing transmembrane and cytoplasmic sequences of influenza virus hemagglutinin. Flint however fails to teach or suggest combining E2 with an HBV envelope protein or portions of such a protein in a fusion. One cannot simply extrapolate, as the Office implies (see Office Action, page 7), that fusing residues 384-661 of E2 to viral envelope sequences in general will be broadly applicable to any and all viruses. Contrary to the Office's assertions, it is not predictable that a particular fusion will elicit an immune response against HCV and be capable of assembling into virus particles in the absence of experimental evidence that such a fusion works. The entirely different surface characteristics of influenza virus and HBV, due to, *e.g.*, different proteins in their viral envelopes, are expected to cause the virus particles of

the two viruses to behave differently. One would not have a reasonable expectation of success in producing a fusion of HCV E2 and HBsAg capable of eliciting an immunological response against HCV and assembling into virus particles based on methods described for influenza.

Thus, there is no combination of the cited references that renders the claimed subject matter obvious, and withdrawal of the rejection under 35 U.S.C. § 103(a) is in order.

E. The Claimed Invention is Not Obvious

To reiterate, a determination of obviousness is not appropriate just because bits and pieces of the claimed invention can be found in several references. Rather, statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. See, e.g., *KSR*, page 14 and *In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000). Indeed, the fact that the Office relies on a minimum of **six** references and in some cases as many as **ten** references in the stated combinations is probative in and of itself of non-obviousness!

Moreover, the primary reference of Major fails to describe or suggest a nucleic acid encoding a fusion protein combining an HBsAg polypeptide and an E2 polypeptide, as claimed. There can be no reasonable expectation of success that a fusion containing an E2 antigen could be expressed at sufficient levels to invoke an immune response against HCV or that such a fusion would be incorporated into HBV virus particles based on the behavior of an HBsAg fusion with another protein, such as the HCV core protein. Additionally, HBsAg fusions with other completely unrelated proteins, as described by Jacobs and Valenzuela, also fail to predict the behavior of an HBsAg fusion with E2. Nor is it obvious that the same sequence of E2 used with an influenza viral envelope sequence would work with an HBV viral sequence.

In contrast, applicants have provided experimental evidence that expression of a nucleic acid encoding a fusion protein comprising the sequence of SEQ ID NO:7 and HBsAg elicits and immune response in mice (see Example 5) and results in formation of

virus-like particles (see Examples 2 and 4). Applicants again emphasize that this is a result not readily predictable from any of the cited references.

For at least these reasons, withdrawal of all of the foregoing rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, applicants submit the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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